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TITLE: Modulators of molecules with phosphotyrosine recognition units

BSPR:
In an early study, vanadate was found to inhibit protein-tyrosine phosphatases in mammalian cells with a concomitant increase in the level of phosphotyrosine in cellular proteins leading to transformation (Klarlund, Cell 41: 707-717 (1985)). Vanadium-based phosphatase inhibitors are relatively unspecific. Therefore, to assess the importance of specific structures on PTPase activity more selective inhibitors are needed. One possibility for obtaining selective PTPase inhibitors would be through design of different ancillary ligands for peroxovanadium-based compounds (Posner et al., J. Biol. Chem. 269:4596-4604 (1994)). Another avenue taken by several investigators has been to incorporate nonhydrolyzable tyrosine phosphate analogs into specific peptide substrates: (1) phosphonomethyl phenylalanine (Zhang et al., Biochemistry 33: 2285-2290 (1994)); (2) difluorophosphono-methyl phenylalanine Burk et al., Synthesis 11: 1019-1020 (1991)); (3) L-O-malonyltyrosine (Kole et al., Biochem. Biophys. Res. Commun. 209: 817-822 (1995)); (4) cinnamic acid (Moran et al., J. Am. Chem. Soc. 117: 10787-10788 (1995); Cao et al., Bioorganic Med. Chem. Lett. 5: 2953-2958 (1995)); (5) sulfotyrosyl (Liotta et al., J. Biol. Chem. 269: 22996-23001 (1994)). A surprising degree of selectivity is observed with simple peptide analogs containing phosphonodifluoromethyl phenylalanine as a substitute for tyrosine (Chen et al., Biochem. Biophys. Res. Commun. 216: 976-984 (1995)). Important information has further been obtained with synthetic peptides containing sulfotyrosyl residues. A synthetic peptide corresponding to the amino acid sequence of a defined loop of the insulin receptor tyrosine kinase, Thr-Arg-Asp-Ile-Xxx-Glu-Thr-Asp-Xxx-Xxx-Arg-Lys (SEQ ID NO:3) (where Xxx denotes sulfotyrosyl), acts as a PTPase inhibitor (Liotta et al., 1994, supra). More importantly, this peptide, when tagged with stearic acid can penetrate cells, and stimulate the action of insulin (Liotta et al., 1994, supra).

BSPR:
Relatively little is known about the identity of the PTPases involved in IRTK regulation. However, the existence of PTPases with activity towards the insulin receptor can be demonstrated as indicated above. Further, when the strong PTPase-inhibitor pervanadate is added to whole cells an almost full insulin response can be obtained in adipocytes (Fantus et al., Biochemistry 28: 8864-8871 (1989); Eriksson et al., Diabetologia 39: 235-242 (1995)) and skeletal muscle (Leighton et al., Biochem. J. 276: 289-292 (1991)). In addition, recent studies show that a new class of peroxovanadium compounds act as potent hypoglycemic compounds in vivo (Posner et al.,supra). Two of these compounds were demonstrated to be more potent inhibitors of dephosphorylation of the insulin receptor than of the EGF-receptor.